

WHAT IS CLAIMED:

1. A method for identifying an analyte which is a histone deacetylase (HDAC) inhibitor, which comprises:

5 (a) providing cells which include a reporter gene encoding an enzyme operably linked to a transcription regulatory sequence which includes nucleotide sequences responsive to a known HDAC inhibitor or HDAC subtype stably integrated into the genome of the cells;

(b) culturing the cells in a medium which includes the analyte and a substrate for the enzyme; and

10 (c) measuring activity of the enzyme on the substrate wherein an increase in the activity of the enzyme on the substrate indicates that the analyte is an HDAC inhibitor.

2. The method of Claim 1 wherein the cells are mammalian cells.

15 3. The method of Claim 1 wherein the cells are human cells.

4. The method of Claim 1 wherein the cells are selected from the group consisting of HeLa cells and MCF7 cells.

20 5. The method of Claim 1 wherein the cells are ICLC PD02008.

6. The method of Claim 1 wherein the transcription regulatory sequence includes a transcription regulatory sequence of p21^{WAF1/CIP1} which does not include nucleotide sequences responsive to p53.

25 7. The method of Claim 6 wherein the p21^{WAF1/CIP1} transcription regulatory sequence includes from about nucleotide -183 to nucleotide +25 of the p21^{WAF1/CIP1} transcription regulatory sequence.

30 8. The method of Claim 6 wherein the p21^{WAF1/CIP1} transcription regulatory sequence includes the nucleotide sequence set forth in SEQ ID NO:1.

9. The method of Claim 1 wherein the known HDAC inhibitor is selected from the group consisting of Apicidin, Trichostatin A, sodium butyrate, SAHA, and MS27-275.

10. The method of Claim 1 wherein the reporter gene encodes β -lactamase.

11. The method of Claim 10 wherein the substrate for the β -lactamase includes a cephalosporin cleavage site.

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12. The method of Claim 1 or 10 wherein the substrate is labeled with a donor:acceptor fluorophore pair which is capable of fluorescence resonance energy transfer.

10 13. A cell comprising a reporter gene encoding an enzyme operably linked to a transcription regulatory sequence which includes nucleotide sequences responsive to a known histone deacetylase (HDAC) inhibitor or HDAC subtype stably integrated into the genome of the cell.

15 14. The cell of Claim 13 wherein the reporter gene is operably linked to a p21^{WAF1/CIP1} transcription regulatory sequence which includes nucleotide sequences responsive to a histone deacetylase (HDAC) inhibitor selected from the group consisting of Apicidin, Trichostatin A, sodium butyrate, SAHA, and MS27-275 and not nucleotide sequences responsive to p53 stably integrated into the genome of the cell.

20 15. The cell of Claim 13 or 14 wherein the cell does not have a functional p53.

16. The cell of Claim 13 or 14 wherein the cell is selected from the group consisting of HeLa cells and MCF7 cells.

25 17. The cell of Claim 14 wherein the cell is ICLC PD02008.

18. The cell of Claim 14 wherein the p21^{WAF1/CIP1} transcription regulatory sequence includes the nucleotide sequence from about nucleotide -183 to nucleotide +25 of the p21^{WAF1/CIP1} transcription regulatory sequence.

30 19. The cell of Claim 14 wherein the p21^{WAF1/CIP1} transcription regulatory sequence includes the nucleotide sequence set forth in SEQ ID NO: 1.

20. The cell of Claim 13 or 14 wherein the reporter gene encodes β -lactamase.

21. A plasmid comprising a gene encoding β -lactamase operably linked to a transcription regulatory sequence which includes nucleotide sequences responsive to a histone deacetylase (HDAC) inhibitor or HDAC subtype.

5 22. The plasmid of Claim 21 wherein the gene encoding the β -lactamase is operably linked to a p21^{WAF1/CIP1} transcription regulatory sequence which includes nucleotide sequences responsive to a histone deacetylase (HDAC) inhibitor selected from the group consisting of Apicidin, Trichostatin A, sodium butyrate, SAHA, and MS27-275 and not nucleotide sequences responsive to p53.

10 23. A method for treating a cancer in a patient, which comprises:

(a) providing one or more cultures of cells which include a reporter gene operably linked to a transcription regulatory sequence which includes nucleotide sequences responsive to a histone deacetylase (HDAC) inhibitor or HDAC subtype stably integrated into the genome of the cells;

15 (b) culturing each of the one or more cultures of cells in a medium which contains an analyte;

(c) identifying the analytes which stimulate expression of the reporter gene in the cells; and

(d) administering one or more of the analytes identified in step (c) to stimulate expression of the reporter gene to the patient to treat the cancer.

20 24. The method of Claim 23 wherein the transcription regulatory sequence is a p21^{WAF1/CIP1} transcription regulatory sequence which includes nucleotide sequences responsive to a histone deacetylase (HDAC) inhibitor selected from the group consisting of Apicidin, Trichostatin A, sodium butyrate, SAHA, and MS27-275 and not nucleotide sequences responsive to p53.

25 25. A method for inducing differentiation or apoptosis of a proliferative cell, which comprises:

30 (a) providing one or more cultures of cells which include a reporter gene operably linked to a transcription regulatory sequence which includes nucleotide sequences responsive to a histone deacetylase (HDAC) inhibitor or HDAC subtype stably integrated into the genome of the cells;

(b) culturing each of the one or more cultures of cells in a medium which contains an analyte;

(c) identifying the analytes which stimulate expression of the reporter gene in the cells; and

(d) administering one or more of the analytes identified in step (c) to stimulate expression of the reporter gene to the proliferative cell to induce the differentiation or apoptosis of the proliferative cell.

5 26. The method of Claim 25 wherein the transcription regulatory sequence is a p21WAF1/CIP1 transcription regulatory sequence which includes nucleotide sequences responsive to a histone deacetylase (HDAC) inhibitor selected from the group consisting of Apicidin, Trichostatin A, sodium butyrate, SAHA, and MS27-275 and not nucleotide sequences responsive to p53.

10 27. A kit, which comprises cells which include a reporter gene operably linked to a transcription regulatory sequence which includes nucleotide sequences responsive to a known histone deacetylase (HDAC) inhibitor integrated into the genome of the cells.

15 28. The kit of Claim 27 further comprising a substrate for the reporter gene.

29. A method for identifying analytes which are histone deacetylase (HDAC) inhibitors, which comprises:

20 (a) providing one or more cultures of cells which include a reporter gene encoding an enzyme operably linked to a transcription regulatory sequence responsive to an HDAC inhibitor or HDAC subtype stably integrated into the genome of the cells;

 (b) culturing each of the one or more cultures of recombinant cells in a medium which contains an analyte; and

 (c) identifying the analytes which stimulate expression of the reporter gene in the cells, wherein analytes which stimulate expression of the reporter gene are HDAC inhibitors.

25 30. The method of Claim 29 wherein the transcription regulatory sequence consists essentially of the transcription regulatory sequence from about nucleotide -183 to nucleotide +25 of the p21WAF1/CIP1 transcription regulatory sequence.

30 30. A method for identifying an analyte which is a histone deacetylase (HDAC) inhibitor, which comprises:

 (a) providing cells which include a reporter gene encoding an enzyme operably linked to a transcription regulatory sequence which includes nucleotide sequences responsive to a known HDAC inhibitor or HDAC subtype stably integrated into the genome of the cells; and

(b) measuring expression of the reporter gene wherein an increase in expression of the reporter gene indicates that the analyte is an HDAC inhibitor.

31. A method for identifying an analyte which is a histone deacetylase (HDAC) inhibitor, which comprises:

(a) providing a transcription regulatory sequence of a gene which is responsive to a known HDAC;

(b) constructing a gene expression cassette comprising a reporter gene encoding an enzyme operably linked to the transcription regulatory sequence of the gene;

(c) transfecting a cell with the gene expression to produce a cell which includes the gene expression cassette stably integrated into the genome of the cell;

(d) providing a multiplicity of the cell in a medium which includes the analyte and a substrate for the enzyme; and

(e) measuring activity of the enzyme on the substrate wherein an increase in the activity of the enzyme on the substrate indicates that the analyte is an HDAC inhibitor.

32. A method for identifying an analyte which is a histone deacetylase (HDAC) inhibitor, which comprises:

(a) providing cells which include a reporter gene encoding an enzyme operably linked to a transcription regulatory sequence which includes nucleotide sequences responsive to a known HDAC stably integrated into the genome of the cells;

(b) culturing the cells in a medium which includes the analyte and a substrate for the enzyme; and

(c) measuring activity of the enzyme on the substrate wherein an increase in the activity of the enzyme on the substrate indicates that the analyte is an HDAC inhibitor.